Attachments following last page of this Amendment:

Abstract (1 page)

REMARKS

Claims 1-32 are pending and under consideration. Claims 1, 14, and 25 have been amended to correct antecedent basis. Claims 14 and 25 have been amended to correct antecedent basis and not to overcome rejections. Claims 5 and 18 have been amended to correct claim dependency and not to overcome rejections. Claims 8, 14, 23, and 25 have been amended to correct typographical errors and not to overcome rejections. New claims 33-40 have been added. Support for these claims can be found in Applicant's specification at, for example, paragraphs [0051], [0054], and [0061] – [0063]. No new matter is entered by way of these amendments. Applicants request that all claims be examined in view of the amendment to the claims.

Abstract Objection

The abstract was objected to for allegedly failing to be presented in proper domestic form. Applicants interpret this objection to mean that a numbered page containing the abstract only was not included with the copy of the international application. Instead, the face page of the PCT publication was submitted as the abstract. The Examiner is invited to contact the Applicants' undersigned representative if the Applicants misinterpreted this objection.

A replacement abstract is filed with this response to correct the informalities to comply with the requirements of the Patent Office. No new matter has been added. Applicants respectfully request withdrawal of this objection.

35 U.S.C. § 112, first paragraph

Claims 1-32 were rejected for allegedly not being enabled. Specifically, the Office Action states that the claims encompass an immense number of species having a wide variety of structural formulas; that guanidine substituted aminoglycosides are known in the prior art; that it is well known that minor changes in a compound's structural formula can alter its activity; that the disclosure of guanidine-tobramycin and guanidine-neomycin conjugated to BODIPY or Florescin is not commensurate with the full scope of the claims; that there are no examples of

active compounds conjugated to guanidine-tobramycin or guanidine-neomycin; and that it would take undue experimentation to test various compounds encompassed by the claims.

Applicants respectfully disagree. The test of enablement is whether the specification teaches one skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Thus, the enablement analysis must be focused on the product or method defined by the claims. Importantly, "a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 439 F.2d 220, 222-223 (CCPA 1971) (emphasis in the original). The Examiner bears the burden of "providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement." *In re Wright*, 999 F.2d at 1561 (Fed. Cir. 1993). The Examiner has not met his burden in the present case.

Claim 1, as amended, recites a composition comprising a beneficial compound conjugated to an adduct of a dialkoxy substance and a guandinylating reagent. The Office Action states that the claims include an immense number of species with a wide variety of specific structural formulas and concludes that the specification would not have taught one skilled in the art how to make and/or use the claimed invention. Applicants respectfully disagree. While there are several options for the composition components, the specification provides specific details on each component and methods for connecting each of these components to produce the claimed compounds. Paragraph [0052] notes that the conjugates can be prepared by separately synthesizing the various components and coupling the individual components together in advanced stages. For example, the adduct formed from the dialkoxy substance and the guanidinylating reagent is a guanidinylated dialkoxy substance that can be *fully* guanidinylated (i.e., all primary or secondary amines of the dialkoxy substance are

converted into guadinine groups). See, for example, paragraph [0051] of the present application and U.S. Patent No. 6,833,445.

The specification provides several references in the art that describe methods of synthesizing guanidinylated dialkoxy substances as well as examples of this process. See paragraphs [0051], [0058], [0061], [0063]; Schemes 1, 2, 3, and 6; and Examples 1 and 2. Further, the specification describes methods of conjugating a beneficial compound to the adduct. For example, the adduct can be conjugated to the beneficial compound through a linker attached to the adduct. The specification and amended claims provide types of linkers that can be used to conjugate the adduct to the beneficial compound, including releasable linkers, thiol linkers, amine linkers, and amino acid linkers. See claims 33-40; paragraphs [0051], [0053], [0054] to [0056], and [0061] to [0063]; Schemes 1 and 6; and Example 2. Applicants respectfully note that an inventor "need not, however, explain every detail since he is speaking to those skilled in the art." *In re Howarth*, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981). As the Federal Circuit has held, "[n]ot every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be." *In re Gay*, 309 F.2d 769, 774, 50 CCPA 725, 733, 135 USPQ 311, 316 (CCPA 1962). The specification provides sufficient detail for one of ordinary skill in the art to make the claimed compositions; thus, the claims are enabled by the specification as filed.

The Office Action states that guanidino substituted aminoglycosides are known in the prior art and cites U.S. Patent No. 6,525,182 as evidence. Applicants agree that examples of preparing guanidino substituted aminoglycosides are described in U.S. Patent No. 6,525,182, which further supports that one of skill in the art knows how to make the adducts formed from the dialkoxy substance and the guanidinylating reagent. The compounds described in U.S. Patent No. 6,525,182 are examples of the adducts of a dialkoxy substance and a guanidinylating reagent that can be used to prepare the claimed conjugates, not examples of the claimed conjugates used in the compositions. The Office Action also states that minor changes in the structural formula of a compound can alter the compound's activity. However, methods for evaluating the activity of the beneficial compound prior to conjugation with the adduct and after

conjugation with the adduct are well known to those of skill in the art. Thus, one of skill in the art would know how to evaluate the activity of the conjugated compound to determine whether the beneficial compound's activity has been altered without undue experimentation.

The Office Action states that the disclosure of guanidine-tobramycin and guanidine-neomycin conjugated to BODIPY or Florescin is not commensurate with the full scope of the claims and that no examples of beneficial compounds conjugated to the adducts are provided. However, paragraph [0051] and Scheme 1 clearly describe a process and synthetic route for producing a guanidine-neomycin B adduct conjugated to AZT, an active HIV reverse transcriptase inhibitor. Paragraphs [0052] to [0056] further describe the linkers used to conjugate the adduct and AZT, thus providing a fully enabling description of methods of linking the components.

Further, the Office Action states that an enormous amount of trial and error to test various compounds encompassed by the claims would be required as there is no way to predict the cellular uptake of the compounds. As stated in the M.P.E.P. § 2164.06, the test for enablement is "not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976). The specification of the present application provides such guidance. Example 11 of the present application describes a method of evaluating the AZT-guanidino-neomycin B conjugate for increased cellular uptake. Further, it is known to one of ordinary skill in the art that labeling experiments would also reveal this information. Suitable labels, methods of producing labeled conjugates, and tools for analyzing labeling experiments are provided in paragraphs [0072] to [0074]. Example 10 also provides an example that one of skill in the art would know is useful for determining the cellular uptake of compounds. Thus, one of skill in the art would know how to make and/or use the full scope of the claims without undue experimentation.

In summary, the present claims are enabled by the specification as filed. Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

35 U.S.C. § 112, second paragraph

Claims 1-32 were rejected for allegedly being indefinite. Specifically, the Office Action recites that the structural formulas of the claimed compounds are unclear for not showing how the components of the composition are attached. The Office Action also states that the use of the term "comprise[s]" renders claims 3 and 4 indefinite for leaving the structural formula of the claimed compound open-ended. Additionally, claims 9 and 10 were rejected for allegedly lacking antecedent basis. Further, claims 14-32 were rejected for allegedly omitting essential steps. Applicants respectfully traverse these rejections.

Applicants assert claims 1-32 are definite and distinctly claim the subject matter and that the structural formulas of the compositions are clear. The test for definiteness under 35 U.S.C. § 112, second paragraph, is whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification." *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). According to M.P.E.P. § 2173.05(t), "a claim to a chemical compound is not indefinite merely because a structure is not presented or because a partial structure is presented." M.P.E.P. § 2173.04 notes that the "breadth of a claim is not to be equated with indefiniteness." The present claims, when read in light of the specification, are clear and understandable by those of skill in the art, as detailed herein.

Claim 1, as amended, recites a composition comprising a beneficial compound conjugated to an adduct of a dialkoxy substance and a guandinylating reagent. First, a person of ordinary skill in the art would understand from reading the specification that an adduct formed from a dialkoxy substance and a guanidinylating reagent is structurally described. For example, the adduct formed due to the reaction of a guanidinylating reagent and a glycoside as the dialkoxy compound is termed a "guanidinoglycoside." See paragraph [0036] of the present application. A guanidinoglycoside can be characterized as a "fully guanidinylated analogue" in which each primary or secondary amine of the glycoside is converted into a guadinine group.

See, for example, paragraph [0051] of the present application and U.S. Patent No. 6,833,445. Further, the specification provides several references in the art that describe methods of synthesizing guanidinylated dialkoxy substances. See paragraph [0051] of the present application. Paragraph [0058] provides several examples of dialkoxy compounds that may be guanidinylated and Schemes 1, 2, 3, 6, and 9 each provide synthetic schemes that illustrate the various sites of attachment of the dialkoxy substance to the guanidinylating reagent as defined in the specification. The reaction of the guanidinylating reagent and the dialkoxy substance is further described in paragraphs [0061] and [0063]: "The Boc groups can be then removed and the free amines can be reacted with a Boc-protected guanidylating reagent." Examples 2 and 4 provide detailed reaction protocols for producing the adduct.

Further, as a person of ordinary skill in the art would understand, the conjugation of a beneficial compound to the adduct is also structurally described in the claims and the specification of the present application. Claims 7 and 24 as originally filed recite that the beneficial compound in the conjugate is covalently bonded to the adduct. One of ordinary skill in the art has knowledge of reactive sites on the beneficial compound and the adduct. Further, the person of ordinary skill in the art has knowledge of structure-function relationships. Thus, those of skill in the art can use this information to determine the positions of the beneficial compound and the adduct to modify. The person of skill in the art is further guided regarding the positions to modify through evaluating the activity of the compounds, as discussed above. Thus, a person of ordinary skill in the art would understand how to covalently bond the beneficial compound to the adduct.

The specification and claims provide additional guidance for conjugating the beneficial compound to the adduct. Claims 33 and 37, scheme 1, and paragraph [0051] note that the adduct can be conjugated to the beneficial compound through a linker. Paragraph [0052] notes that the conjugate design allows for the mixing-and-matching of various carriers/RRE binders with a variety of linkers and NRTI monophosphates and paragraphs [0053] and [0054] provide examples of this mixing-and-matching. A type of linker for use in making the compositions is provided in paragraph [0056]. Further examples of linkers for use in preparing the conjugates,

including amine linkers and thiol linkers, are provided in claims 35, 36, 39, and 40 and paragraphs [0061] through [0063]. Example 2 and Scheme 6 provide detailed reaction protocols for producing the conjugate. Therefore, those of skill in the art would understand what is claimed when the claim is read in light of the specification. Thus, Applicants respectfully request reconsideration and withdrawal of the rejection.

Claims 3 and 4 were rejected as allegedly being indefinite for use of the term "comprises[s]" and leaving the structural formula open-ended. Applicants respectfully traverse this rejection. The structures of chemical compounds should not be considered indefinite nor speculative in the absence of evidence that the assigned formula is in error. See M.P.E.P § 2173.05(t). Applicants assert that the assigned formula is not in error; thus, the indefiniteness rejection is improper. Further, as noted above, according to M.P.E.P. § 2173.05(t), "a claim to a chemical compound is not indefinite merely because a structure is not presented or because a partial structure is presented." M.P.E.P. § 2173.04 notes that the "breadth of a claim is not to be equated with indefiniteness." As discussed above, one of skill in the art would have knowledge of how these components are attached to form the conjugates based on knowledge of reactive sites on the components and structure-function activity relationships. Thus, the use of the term "comprise[s]" in claims 3 and 4 is appropriate. Applicants assert that the rejection is improper and respectfully request reconsideration and withdrawal of the rejection

Claims 9 and 10 were rejected as allegedly being indefinite for use of the term "beneficial compound," which lacks antecedent basis. Claim 1, the independent claim that claims 9 and 10 depend from, has been amended to recite "beneficial compound" instead of "compound" to correct antecedent basis.

Claims 14-32 were rejected as allegedly being indefinite for omitting essential steps. Specifically, the Office Action (page 4, second paragraph) states that the specific treating and conjugated steps are omitted and that no reaction steps are provided. Applicants respectfully traverse this rejection. The M.P.E.P. provides that "a claim which fails to interrelate essential elements of the invention as defined by applicant(s) in the specification may be rejected under 35 U.S.C. § 112, second paragraph." M.P.E.P. § 2172.01. Applicants assert that independent claim

14 interrelates the essential elements of a method of increasing the cellular uptake of a beneficial compound.

The method of increasing the cellular uptake of a beneficial compound as described in claim 14 and paragraph 41 of the specification includes forming a conjugate including the beneficial compound and delivering the conjugate to a cell. Steps (a) and (b) recite the essential elements for forming the conjugate: "(a) modifying a dialkoxy substance by treating the dialkoxy substance with a guanidinylating reagent to form an adduct" and "(b) conjugating the adduct with the beneficial compound to form a conjugate." Thus, there is no omission between these two steps and the essential elements are interrelated as the first step provides a reaction to form an adduct and the second step provides the reaction of conjugating the adduct with the beneficial compound to form the conjugate.

Applicants also assert that specific reaction steps are provided in claim 14. The step of modifying the dialkoxy substance involves a reaction between the dialkoxy substance with a guanidinylating reagent. The step of forming the conjugate involves a reaction (i.e., a conjugation reaction) between the adduct and a beneficial compound. As stated above, all that is required for a claim to meet the test for definiteness under 35 U.S.C. § 112, second paragraph, is that "those skilled in the art would understand what is claimed when the claim is read in light of the specification." *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). One of skill in the art would understand that the conjugates to be delivered to a cell are prepared from a dialkoxy substance, a guanidinylating reagent, and a beneficial compound according to the reactions described in claim 14 and the specification, as detailed above. Further, one of skill in the art would have knowledge of methods of attaching these components to form the conjugates based on knowledge of reactive sites on the components and structure-function activity relationships. Therefore, the essential elements of the method are defined and interrelated in claim 14 and its dependent claims thereon.

In summary, those of skill in the art would understand what is claimed when the claims as a whole are read in light of the specification. Applicants respectfully request reconsideration and withdrawal of the rejections of claims 1-32 under 35 U.S.C. § 112, second paragraph.

CONCLUSION

Applicants respectfully assert that the claims are in condition for allowance, which action is hereby requested. The Examiner is invited to telephone the undersigned attorney if such would expedite prosecution.

Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: December 30, 2009

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